“Metabolic Syndrome”

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“Metabolic Syndrome” Outline

- History
- Definition
- “Metabolic syndrome” verses “insulin resistance syndrome”
- How insulin resistance causes disease
- Treatment of “metabolic syndrome”

Caution: This is going to get confusing.

- Different Definitions for “Metabolic Syndrome”.
  - WHO verses ATP III definitions
- Similar terms that have unique definitions.
  - Metabolic Syndrome verses Insulin Resistance Syndrome
- Controversy about value of the term “Metabolic Syndrome”.
  - ADA position paper (September 2005 Diabetes Care)
- A lot of unknowns out there.

History

- CVD is the major cause of mortality.
- Clustering of Risk Factors For CVD: obesity, Type 2 DM, HLP and HTN.
- Unifying Hypothesis: Insulin Resistance and compensatory hyperinsulinemia predisposed patients to conditions.
- Synonyms (?):
  - Syndrome X
  - Insulin resistance syndrome
  - Metabolic syndrome
  - Beer-belly syndrome
  - Dysmetabolic syndrome
  - Reaven's syndrome

History

- "Metabolic Syndrome" is now institutionalized
  - 1998 - WHO definition – Focused on insulin resistance.
  - 2001 - Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) definition focused on abdominal obesity
  - ICD-9 code (277.7)
- It represents a constellation of risk factors for CVD

Metabolic Syndrome -WHO

Diabetes, IFG, IGT, or insulin resistance (assessed by clamp studies) **and** at least two of the following criteria:

1) waist-to-hip ratio >0.90 in men or >0.85 in women

2) serum triglycerides 1.7 mmol/l or HDL cholesterol <0.9 mmol/l in men and <1.0 mmol/l in women

3) blood pressure 140/90 mmHg

4) urinary albumin excretion rate >20 µg/min or albumin-to-creatinine ratio 30 mg/g

Metabolic Syndrome – ATP-III

Elements of Metabolic Syndrome (3 required)

- Abdominal Obesity
  - men > 40 inches
  - women > 35 inches
- Low HDL-C
  - men < 40 mg/dL
  - women < 50 mg/dL
- Elevated Tg (>150 mg/dL)
- Elevated BP (130/85)
- Elevated fasting glucose (>110 mg/dL)

ATP III - http://www.nhlbi.nih.gov/guidelines/cholesterol/

Metabolic vs. Insulin Resistance Syndrome

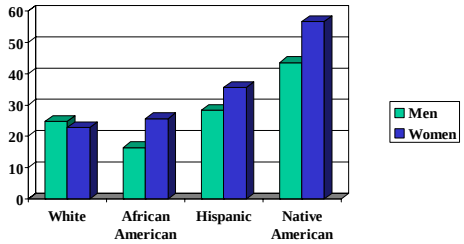
Metabolic Syndrome

- Cardiology Concept
- A constellation of risk factors for **cardiovascular disease**.
- The purpose of the concept is to heighten awareness of risks associated with obesity and sedentary life habits.

Insulin Resistance Syndrome

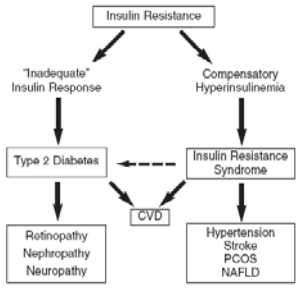
- Endocrinology Concept
- Describes a physiologic state that increases chances of:
  - Type 2 DM
  - CVD
  - HTN
  - PCOS
  - NASH
  - Sleep Apnea

Prevalence of Metabolic Syndrome



Ford ES. Prevalence of the metabolic syndrome among US adults. JAMA 2002;287(3):356-9

Insulin Resistance Syndrome



ACE Position Statement on the Insulin Resistance Syndrome, *Endocr Pract.* 2003;9(No. 3)

ACE Position Statement on the Insulin Resistance Syndrome

Factors That Increase the Likelihood of the Insulin Resistance Syndrome

- Diagnosis of CVD, hypertension, PCOS, NAFLD, or acanthosis nigricans
- Family history of type 2 diabetes, hypertension, or CVD
- History of gestational diabetes or glucose intolerance
- Non-Caucasian ethnicity
- Sedentary lifestyle
- BMI >25.0 kg/m² (or waist circumference >40 inches in men, >35 inches in women)
- Age >40 years

***Endocr Pract.* 2003;9(No. 3)**

ACE Position Statement on the Insulin Resistance Syndrome
If two or more present = IRS

Identifying Abnormalities of the Insulin Resistance Syndrome

1.	Triglycerides	>150 mg/dL
2.	HDL cholesterol	
	Men	< 40 mg/dL
	Women	< 50 mg/dL
3.	Blood pressure	>130/85 mm Hg
4.	Glucose	
	Fasting	110-125 mg/dL
	120 min post-glucose challenge	140-200 mg/dL

***Endocr Pract.* 2003;9(No. 3)**

Prevalence of Variables In IRS

Prevalence of the 4 Abnormalities of the Insulin Resistance Syndrome in NHANES III*

Variable	Prevalence (%)
TG> 150 mg/dL	35
Low HDL-C	36
Hypertension	44
120 min glucose >140 mg/dL	26

*The population includes 3280 individuals, aged 40-74, without diabetes by history or a fasting plasma glucose concentration >126 mg/dL.

	Abnormalities			
	1	2	3	4
Total population (n=3280)	71%	42%	17%	4.5%

ACE Position Statement on the Insulin Resistance Syndrome, *Endocr Pract.* 2003;9(No. 3)

Key Concepts
Insulin Resistance

- A multigenetic condition that is aggravated by obesity.
- Leads to compensatory hyperinsulinemia.
- Muscle and adipose tissue express the insulin resistance.
- Other tissues may remain insulin sensitive.

Pathophysiology of IRS

- Adipose tissue role in IRS
- Lipid abnormalities
- Hypertension
- Polycystic ovary disease
- Nonalcoholic fatty liver disease

Products of Adipose Tissue

- Free fatty acid (FFA)
  - Lipolysis is the breakdown of stored fat into FFA.
  - Insulin suppresses lipolysis.
  - In states of insulin resistance (caused by genetic and environmental factors), FFA secretion is increased.
  - FFA are taken up by the liver.
  - The liver packages FFA into TG rich lipoproteins (VLDL).
  - This leads to hypertriglyceridemia.
  - Metabolism of high levels of VLDL lead to drops in HDL concentrations, as well as, small dense more atherogenic LDL particles.

Products of Adipose Tissue

- Inflammatory cytokines (TNF alpha and IL-6)
  - Enhance endothelial inflammation
  - Increased CRP
- Plasminogen activator inhibitor 1 (PAI-1) - Prothrombotic substance
- Adiponectin – Adipose tissue product that fights insulin resistance. Decreased in obesity.
- Leptin –Obesity is associated with "leptin resistance"

Hypertension

- Despite insulin resistance in adipose tissue and muscles, the kidneys remains insulin sensitive.
- High insulin levels increases renal sodium retention.
- 50% of patients with essential hypertension have insulin resistance.
- Insulin resistance patients with HTN are at greater risk of CVD than non-insulin resistant patients.

Polycystic Ovary Disease

- Sex specific metabolic syndrome “Syndrome XX”
- 5-10% prevalence.
- Multigenetic disorder characterized by hyperandrogenemia and **insulin resistance**.
- Muscle and adipose cells are resistant to insulin leading to hyperinsulinemia, ovary is normal responsive to insulin. Leads to greater ovarian testosterone production.
- Insulin sensitizers work well for therapy.

Polycystic Ovary Disease
High risk of other insulin resistant problems

- Glucose metabolism
  - By 4th decade patients have
    - 35% risk of IGT
    - 10% risk of DM2
- Sleep Apnea
- Lipid abnormalities
- Coronary artery disease

Nonalcoholic Fatty Liver Disease (NASH)

- Resistance of insulin action on adipose tissue leads to increased FFA release.
- If the liver takes up these FFA, converts them to TG but lags behind in packaging the TG in VLDL particles, fatty liver results.
- NASH correlates better with insulin resistance than obesity.

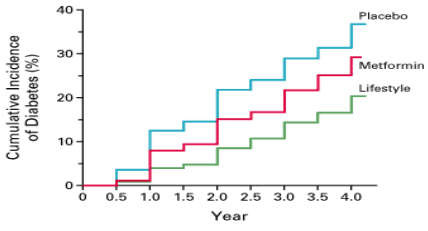
Treatment

Diabetes Prevention Program Research Group

- 3234 adults patients with IGT + BMI>24
  - Metformin 850 mg bid
  - Placebo
  - Intensive lifestyle intervention
- Intensive lifestyle intervention – 16 lesson curriculum on diet, exercise, and behavior modification. Goal >7% weight reduction.

NEJM, 2002, 346:393-403

Diabetes Prevention Program Research Group



NEJM, 2002, 346:393-403

Treatment Recommendations

- Key: Diet and exercise
- Treatment of individual risk factors for CVD
  - Aspirin
  - Hypertension
  - Hyperlipidemia
- Special Situations
  - PCOS - Insulin sensitizers
  - NASH – Insulin sensitizers
- General Use of Insulin Sensitizers ?

Summary of concerns regarding the metabolic syndrome

1) Criteria are ambiguous or incomplete. Rationale for thresholds are ill defined.

2) Value of including diabetes in the definition is questionable.

3) Insulin resistance as the unifying etiology is uncertain.

4) No clear basis for including/excluding other CVD risk factors.

5) CVD risk value is variable and dependent on the specific risk factors present.

6) The CVD risk associated with the "syndrome" appears to be no greater than the sum of its parts.

7) Treatment of the syndrome is no different than the treatment for each of its components.

8) The medical value of diagnosing the syndrome is unclear.

The Metabolic Syndrome: Time for a Critical Appraisal
ADA Position Statement. Diabetes Care Sept 2005.

"Metabolic Syndrome" Conclusion

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